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Editorial Comment

Ratio of End-Systolic Stress to End-Systolic Volume: Is it a Useful Clinical Tool?*

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The current study by Morgan and colleagues (1) focuses on a central issue in cardiology—the need to evaluate contractility easily. Contractility can be defined as the ability of the heart to generate force at a given preload. Maintenance versus loss of contractility is a key determinant of outcome for most cardiac diseases. It is therefore not surprising that so much effort over the last 30 years has been directed to trying to measure this property clinically.

Role of clinical determination of the end-systolic pressure/volume relation. In the muscle laboratory, the contractility of an isolated piece of cardiac muscle can be measured precisely. The preload (initial fiber length) can be set and the force generated from the ensuing contraction can be accurately measured. Unfortunately, measuring contractility in the intact ventricle is considerably more difficult and measuring it in the intact ventricle in the intact organism is more difficult still. The complexity of the measurement of contractile function in patients with heart disease is at loggerheads with the rules for clinical acceptance of most techniques or measurements. For a technique to be accepted as a clinical tool, it must be relatively easy to use and also provide information that is accurate enough to be helpful in patient management. The difficulties in measuring contractile state in a sick patient with heart disease generate a conflict between some methods of assessing contractile function that are relatively accurate but difficult to apply and other methods that are less accurate but easy to apply. For instance, the end-systolic pressure-volume relation popularized by Suga et al. (2) has undergone intense scrutiny as a method for evaluating contractile function. Despite some well described limitations, the slope of the end-systolic pressure-volume relation has been shown to accurately reflect short-term changes in contractile state (3,4). Unfortunately, the determination of this relation involves measurement of end-systolic volume at several different levels of afterload and includes the assumption that the maneuvers that change load do not also change contractile function. Although these hurdles can be overcome in the laboratory, the need to measure volume at several different loads produced by manipulation of the circulation makes these techniques hard to apply clinically to large groups of ill subjects.

Ejection fraction as an index of contractile function. At the other end of the spectrum, ejection fraction, which is determined in part by contractile function, is easily obtained from a contrast ventriculogram, radionuclide ventriculogram or an echocardiogram. This easily applied index has generally been prognostic of many types of heart disease. Thus, the combination of applicability and relative accuracy has led to its wide acceptance as an index of cardiac function. Unfortunately, ejection fraction not only is determined by contractile function but also is affected by preload and afterload. In situations such as valvular heart disease in which load is abnormal, the ejection fraction may be inaccurate in gauging contractile function. A classic example of this problem is that of a patient with aortic stenosis, a 100 mm Hg transvalvular gradient and an ejection fraction of 15%. Whereas the ejection fraction would predict a poor outcome for such a patient, mechanical relief of the excessive afterload imposed by the stenotic valve is usually associated with an excellent outcome as well as an increase in postoperative ejection fraction. This inaccuracy of ejection fraction in assessing both contractile function and prognosis has led to investigation of other indexes of contractile function.

The ratio of end-systolic pressure or end-systolic stress to end-systolic volume. This ratio is an index of contractile function that derives from a very simple empiric concept: a ventricle that can shorten to a small end-systolic volume at a high end-systolic load is stronger (has more contractility) than a ventricle that remains relatively larger at the end of systole at a similar or lower load (5). In my view, no attempt should be made to extrapolate this empiric device to the concept of Suga et al. (2). Unless the volume of the unloaded ventricle at the end of systole (V_0) was exactly zero (an unlikely event), the simple ratio of afterload to volume cannot and should not be substituted for the slope of the end-systolic pressure-volume relation.

Because the data necessary to develop the ratio are easily obtained, the device is easily applicable as a clinical tool. But how accurate is it? Table 1 (1,6–16) provides a partial list of studies that have compared either the end-systolic pressure/end-systolic volume ratio or the end-systolic stress/end-systolic volume ratio with the more accepted slope of the end-systolic pressure-volume relation or that have at-

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Table 1. Published Studies Comparing Various Indexes of Cardiac Function

Reference	No. of Subjects	Index Examined	Disease	Conclusions
1	8 Dogs	PSP/ESVI: ESS/ESVI	Pacing CMP	Ratio correlated well with rest EF; afterload independence an advantage over EF
6	7 Dogs	MSVR	—	Ratio increased appropriately with inotropic state, but ratio was afterload dependent—varying directly with afterload
7	11 Patients	PSP/ESV	S/P CABG	Ratio was preload independent but increased if afterload increased
8	11 Patients	ESS/ESVI	Sickle cell anemia	Ratio correlated well with slope to the ESPVR
9	11 Patients	ESS/ESVI	Hypertension	Ratio correlated well with slope of the ESPVR
10	21 Patients	ESS/ESVI	MR	Ratio was prognostic of outcome and superior to EF
11	37 Patients	ESS/ESVI	Valvular HD	Ratio predictive of outcome in MR but not for AS or AR
12	76 Patients	PSP/ESVI	MR	Low PSP/ESVI associated with increased mortality but EF was superior in predicting overall clinical outcome
13	33 Patients	PSP/ESVI	CAD	Failure of ratio to increase with exercise correlated with the extent of CAD
14	30 Patients	PSP/ESV	CAD	Ratio was depressed at rest in 71% of patients with CAD and depressed with exercise in 95%
15	243 Patients	PSP/ESV	CAD	Ratio 84% sensitive to CAD during exercise but not superior to EF
16	20 Patients	PSP/ESV	CAD	Ratio responded appropriately to increased inotropic state but was inferior to ESPVR in assessing contractility

AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CMP = cardiomyopathy; EF = ejection fraction; ESPVR = end-systolic pressure-volume relation; ESS = end-systolic stress; EVS = end-systolic volume; ESVI = end-systolic volume index; HD = heart disease; MR = mitral regurgitation; MSVR = maximal stress/volume ratio; PSP = peak systolic pressure; S/P = status post.

tempted to use the ratios to predict clinical outcome. Whereas most investigators found the ratio of stress to volume or pressure to volume useful, others did not. Two factors may help to account for the discrepancies: 1) the tendency for the ratio to be afterload dependent, and 2) the potential inability of the ratio to account for eccentric hypertrophy.

Afterload dependence of the afterload/volume ratio. Although the current study by Morgan and colleagues (1) did not find the ratio of afterload to end-systolic volume to be afterload dependent, other investigators (6,7) did find afterload dependence of the ratio. An explanation for this discrepancy may be found in the mathematical expression of the slope of the end-systolic afterload (expressed as either pressure or wall stress)/end-systolic volume relation (ESAVR): Slope ESAVR = ESA/(ESV − V_0), where ESA = end-systolic pressure or end-systolic stress (afterload), ESV = end-systolic volume and V_0 = volume at zero afterload. In this relation, as afterload in the numerator increases, the denominator (end-systolic volume − V_0) increases so that the quotient remains constant. By failing to take into account V_0 in the simple ratio, the numerator (afterload) increases proportionally more than the denominator (end-systolic volume); thus, the simple ratio of stress to volume increases as afterload increases. The more different V_0 is from zero, the more it will affect the afterload dependence of the ratio. Thus, studies that examined subjects whose V_0 was close to zero would not find the ratio to be afterload dependent, whereas studies involving subjects whose V_0 was either greatly positive or greatly negative would find the ratio to be afterload dependent.

Effects of eccentric hypertrophy. The addition of sarcomeres in series is a normal part of the eccentric hypertrophy process. Eccentric hypertrophy (from mitral regurgitation, for instance) initially causes the end-systolic volume to increase—not because abnormal sarcomeres are failing to shorten to a small volume at the end of systole, but rather because the heart has become larger overall as a result of the addition of normally functioning sarcomeres in series (17). Thus, a high end-systolic volume produced by normally functioning sarcomeres in eccentric hypertrophy could result in a low stress/volume ratio (because volume had increased) without necessarily indicating a depression in contractile function. Although this effect may potentially limit the usefulness of the ratio in mild eccentric hypertrophy, it is apparently not so limiting in very large hearts. Virtually all studies of volume overload have found that end-systolic dimension or end-systolic volume, when increased, is a poor prognostic sign, presumably because contractility is impaired (11,18–20). Concordantly, a very large end-systolic volume produces a low ratio, also suggesting impaired contractility.

Conclusions. The ratio of end-systolic afterload (pressure or stress) to end-systolic volume has been found to be a useful prognostic indicator of the outcome of various types of heart disease by many but not all investigators. The ratio is generally independent of preload and should be superior to ejection fraction as an indicator of contractile function when preload varies widely. Some studies, but not all, suggest that the ratio is afterload dependent and, indeed, a mathematical basis for afterload dependence exists. However, it is probably safe to say that, if afterload is high (a condition that

would tend to artificially raise the ratio) and the ratio is low despite the increased afterload, contractile function is depressed. In our experience, the ratio has been particularly useful in predicting outcome for mitral valve replacement in patients with mitral regurgitation. At present, its exact place in the cardiologist's armamentarium for evaluating patients with heart disease is uncertain. Nevertheless, interest in this ratio has served to emphasize the need for an easily applicable, load-independent index to measure contractile function.

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